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뇌종양 수술을 받는 환자에서 5-aminolevulinic acid 사용여부가 수술 후 간효소 수치에 미치는 영향

2020 년 7 월

서울대학교 대학원

의학과 마취통증의학 전공

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Abstract

Effect of 5-aminolevulinic acid administration for brain tumor surgery on the postoperative liver enzyme level

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Background: Besides 5-aminolevulinic acid (5-ALA), liver enzyme elevation after brain tumor surgery can be caused by anesthesia and medications. In this retrospective study, we determined whether preoperative 5-ALA administration is associated with postoperative elevation of liver enzymes (PELE) in brain tumor patients, and identified predictive factors for PELE in patients treated with 5-ALA. Methods: In 179 patients undergoing brain tumor surgery with

preoperative normal values of liver enzymes, laboratory data on serum alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and total bilirubin (T.bil) levels were collected preoperatively and through the postoperative day (POD) 45. Results: 95 patients received preoperative 5-ALA (5-ALA group), and 84 patients didn't receive 5-ALA (no 5-ALA group). The 5-ALA group had significantly less patients with pulmonary diseases (11[11.6%] vs 21[25.0%], P = 0.032), extracranial malignancy (7[7.4%] vs 27[32.1%], P < 0.001), and had significantly higher preoperative hemoglobin values (14.0 ± 1.3 vs 13.4 ± 1.3, P = 0.002). During the surgery, maximal lactate level (2.2 ± 1.1 vs 1.8 ± 0.8 mmol/L, P = 0.006) was higher, and MBP (73.8 ± 6.6 vs 77.2 ± 6.2 mmHg, P = 0.001) was lower in the 5-ALA group. 99 PELEs (ALT: 56, AST: 34, ALP: 5, and T.BIL: 4) were observed in 62 (34.6%) patients. Four (4.2%) patients treated with 5-ALA showed grade 3 elevation of transaminases based on the Common Terminology Criteria for Adverse Effects. Preoperative 5-ALA treatment was predictive of PELE (odds ratio [95% confidence interval], 2.30[1.14-4.67]; P=0.021). In patients treated with 5-ALA (n=95), 70 PELEs (ALT: 39, AST: 22, ALP: 5, and T.BIL: 4) were observed in 41 (43.2%) patients and significant predictive factors for PELE were preoperative ALT level (1.10[1.04-1.17]; P=0.001) and body mass index (BMI, 1.29[1.08-

1.56]; P=0.006). In patients treated with 5-ALA, 13 and 23 patients, of 39 patients whose maximum postoperative ALT levels > 40 U/L, showed the normal value of serum ALT on PODs 14 and 45, respectively. Only three patients showed ALT elevation > 40 U/L on PODs 15–45, with a downward trend. Conclusions: The use of 5-ALA for brain tumor surgery in patients with preoperative normal values of liver enzymes was associated with increased transient PELE, but a low incidence of severely elevated liver transaminases levels. When 5-ALA is administered to patients with the upper normal value of preoperative serum ALT and overweight, attention is paid to PELE.

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Keywords: 5-aminolevulinic acid; hepatobiliary toxicity; brain tumor surgery; alanine transaminase

Student Number: 2015-30593

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Introduction

High-grade glioma, a malignant neoplasm of the central nervous system, responds poorly to radiotherapy and chemotherapy [25, 28]. Surgical removal of the tumor is, therefore, important in disease treatment. However, complete tumor removal is difficult in clinical practice because the tumor's low degree of differentiation obscures the surgical margins. 5-Aminolevulinic acid (5-ALA) is a precursor of protoporphyrin IX (PpIX). Systemic administration of 5-ALA results in selective PpIX accumulation in high-grade glioma cells. PpIX emits red light under surgical microscope fluorescence, enabling the differentiation of a malignant tumor from normal, functional brain tissue [22]. For this reason, the use of 5-ALA is known to improve the surgical resection of high-grade gliomas [24].

One side effect of 5-ALA is hepatocellular toxicity, which is indicated by increased postoperative activities of liver enzymes, such as alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and total bilirubin (T.bil) [5, 15, 24, 26]. However, all previous studies investigating 5-ALA–induced hepatobiliary dysfunction have at least one weakness. Stummer et al.[24] did not evaluate the incidence and extent of hepatobiliary dysfunction in their comparative study. Otherwise, all other clinical investigations have been conducted only in patients who were administered with 5-ALA [5, 15, 26].

Postoperative elevation of liver enzymes (PELE) after brain tumor surgery can be caused by 5-ALA as well as other multiple factors, such as anesthetics, antibiotics, anti-epileptic drugs, anemia, and intraoperative hypotension [7, 11, 16]. To confirm the detrimental effects of 5-ALA on the hepatobiliary system, multivariate analysis, including data on postoperative liver enzymes in patients with brain tumors who have not received 5-ALA treatment is necessary. Also, various confounding factors mentioned above need to be adjusted in multivariate analysis. However, no study has determined in the multivariate

analysis whether 5-ALA is a significant predictor of PELE in patients undergoing craniotomy for removal of brain tumors. Moreover, no clinical investigation to identify predictive factors of PELE in patients with preoperative 5-ALA administration has yet been done.

In this retrospective study, we determined whether preoperative 5-ALA administration is associated with the development of PELE in patients undergoing craniotomy for brain tumor removal. In addition, we determined which factors were predictive of PELE in patients treated with 5-ALA.

Materials and methods

Patients

This retrospective study was conducted after approval from the Institutional Review Board of Seoul National University Hospital (IRB no. 1811-078-985). We reviewed the electronic medical records of patients who underwent brain tumor surgery between January and December 2017, and who had preoperative liver enzyme levels within normal limits. Adult patients aged 18–80 years were included. Exclusion criteria were anesthesia time < 2 h (i.e., brain tumor biopsy), history of a postoperative medical condition that could cause liver enzyme elevation (i.e., gall bladder stones, cardiopulmonary resuscitation, drug toxicity), failure to collect liver enzyme data through the postoperative day (POD) 45, and porphyria. The requirement for written informed content was waived because of the retrospective design of the study.

Data collection

Enrolled patients were divided into two groups (PELE and no PELE) according to the presence or absence of PELE. Data on demographic characteristics, American Society of Anesthesiologists physical status class, comorbidities, preoperative hemoglobin (Hb) level, preoperative systolic blood pressure (SBP), and mean blood pressure (MBP) in the ward were collected. Intra- and postoperative parameters, including anesthesia duration, surgery duration, doses of propofol and remifentanil used, fluid balance, average SBP and MBP, maximal levels of lactate and glucose, intraoperative transfusion, the incidence of intraoperative vasopressor use and continuous phenylephrine infusion, immediate postoperative Hb level, pathologic diagnosis for brain tumor, and postoperative transfusion were also recorded. Serum ALT, AST, ALP, and T.bil levels were measured preoperatively (T0), immediate postoperatively (T1), and on PODs 1 (T2), 2 (T3), 3–6 (T4), 7–14 (T5), and 15–45 (T6). When liver enzymes were measured repeatedly during the study period (T4–6), the highest value for each enzyme was selected and used for data analysis. In our hospital, the upper limit of normal (ULN) for ALT, AST, ALP, and T.bil is 40 U/L, 40 U/L, 118 U/L, and 1.3 mg/dL, respectively. PELE was defined as postoperative elevation above the reference value of one or multiple liver enzymes. The maximal postoperative liver enzyme values were recorded, and the incidence of patients with PELE was determined. Maximal postoperative liver enzyme values were classified as grade 1 (ALT and AST: >ULN–3.0×ULN, ALP: >ULN–2.5×ULN, T.bil: >ULN–1.5×ULN), grade 2 (ALT and AST: >3.0–5.0×ULN, ALP: >2.5–5.0×ULN, T.bil: >1.5–3.0×ULN), grade 3 (ALT, AST, and ALP: >5.0–20.0×ULN; T.bil: >3.0–10.0×ULN), and grade 4 (ALT, AST and ALP: >20.0×ULN; T.bil: >10.0×ULN) elevation of liver enzymes based on the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) of investigations [21]. In patients who received chemotherapy and/or radiotherapy at about one month postoperatively, only the liver enzymes obtained immediately before the therapy were

entered into the data analysis.

Patient management

All patients were treated with dexamethasone and levetiracetam one day before brain surgery and with cefazolin on the day of surgery. In patients treated with 5-ALA, 5-ALA (20 mg/kg; Gliolan; Medac, Wedel, Germany) was administrated orally 3–8 h before anesthetic induction. Patients were instructed to avoid exposure to ultraviolet light for 24 h after 5-ALA ingestion. In all patients, anesthesia was induced and maintained with total intravenous anesthesia by target-controlled infusion of propofol and remifentanil. Intraoperative target MBP was within 20% of the preoperative values, and a bolus or continuous infusion of phenylephrine was used as a vasopressor. After the surgery, all patients were transferred to the intensive care unit without emergence after brain computed tomography examination. In patients with glioblastoma, the Stupp chemo-radiotherapy regimen was initiated about one month after the surgery.

Statistical analysis and sample size

Continuous variables were compared using Student's *t*-test or the Mann–Whitney *U* test according to the results of the Kolmogorov-Smirnov test. For categorical variables, the chi-squared test or Fisher's exact test was used, according to the frequency. *P* values < 0.05 were considered to be significant. Repeated-measures analysis of variance was performed to determine a significant difference in changes in liver enzyme levels over time within the group. Multivariate regression analysis was used to identify predictive factors of PELE in patients treated with 5-ALA, and variables with *P* values ≤ 0.10 in the univariate analysis were entered into a multivariate logistic regression analysis with the forward stepwise conditional method. Receiver operating characteristic (ROC) curve analysis was

performed to evaluate the diagnostic value of the identified risk factors. The optimal cut-off point was determined by maximizing the sum of sensitivity and specificity. All statistical analyses were conducted using SPSS statistical software for Windows, version 25.0 (IBM, Armonk, NY, USA) and MedCalc software, version 18.6 (MedCalc Software, Ostend, Belgium).

In a previous study, 42% of patients with brain tumors who received 5-ALA preoperatively showed PELE [16]. Assuming the incidence of PELE in this study conducted in mixed patients (patients with 5-ALA treatment and the rest without 5-ALA treatment) would be reduced by 8% compared to that reported in the previous study conducted in only patients with 5-ALA treatment, a minimum of 176 subjects was needed to acquire statistical significance with a confidence level of 95% and a total width of the confidence interval of 0.14.

Results

We screened 215 patients. Thirty-six patients (20 with anesthetic times < 2 h, 13 with incomplete laboratory data, and 3 with abrupt PELE due to cardiac arrest or drug toxicity) were excluded from the study. Finally, a total of 179 patients were included in the analyses.

Analysis according to 5-ALA administration

We first divided the patients into two groups. Ninety-five patients who received preoperative 5-ALA (5-ALA group) and 84 patients who did not receive 5-ALA (no 5-ALA group). The 5-ALA group had significantly less patients with pulmonary diseases (11[11.6%] vs 21[25.0%], P = 0.032) and extracranial malignancy (7[7.4%] vs 27[32.1%], P < 0.001). They had significantly higher preoperative hemoglobin values (14.0 ± 1.3 vs 13.4 ± 1.3, P = 0.002) (Table 1). During the surgery, maximal lactate level (2.2 ± 1.0 vs 1.8

± 0.8 mmol/L, P = 0.006) was higher, and MBP (73.8 ± 6.6 vs 77.2 ± 6.2 mmHg, P = 0.001) was lower in the 5-ALA group. There was significantly many astrocytoma (16[16.8%] vs 2 [2.4%], P=0.001), glioma (8[8.4%] vs 1[1.2%], P = 0.038), glioblastoma (55[57.9%] vs 1[1.2%], P<0.001), oligodendroglioma (10[10.5%] vs 0[0.0%], P = 0.002) patients in 5-ALA group. No 5-ALA group included more meningioma (35[41.7%] vs 1[1.1%], P <0.001), schwannoma (7[8.3%] vs 0[0.0%], P = 0.004) patients (Table 2).

The number of patients who showed one or multiple elevations of postoperative liver enzymes was significantly higher in the 5-ALA group, compared with the no-ALA group (41[43.2%] vs 21[25.0%], P = 0.017).

The number of patients who showed maximum postoperative ALT > 40 U/L was significantly greater in the 5-ALA group. (39[41.1%] vs 17[20.2%], P = 0.005). The numbers of patients who met ALT criteria of grade 1 hepatobiliary toxicity were higher in 5-ALA group (32[33.7%] vs 16[19.0%], P = 0.042). In the 5-ALA group, the numbers of patients who met ALT and AST criteria of grade 3 hepatobiliary toxicity were 4 (4.2%) and 1 (1.1%), respectively (Table 2).

Analysis according to PELE

5-ALA usually more used when the tumor is predicted to be malignant or less differentiated. Therefore, there was a difference in the disease etiology of 5-ALA and no 5-ALA group, inevitably. We decided to perform another analysis, according to the occurrence of PELE. 99 PELEs were observed in 62 (34.6%) patients. Postoperative elevation of ALT, AST, ALP, and T.BIL was shown in 56, 34, 5, and 4 patients, respectively. In patients with 5-ALA treatment, three (3.2%), zero (0.0%), and one (1.1%) patient met the ALT, AST, and both criteria for grade 3 on CTCAE, respectively (Table 3). However, in all four of these patients, the ALT and AST levels had returned to preoperative baseline levels (<ULN) at

T6.

Patients with PELE had a higher body mass index (BMI), preoperative and immediate postoperative Hb concentrations, SBP and MBP in the ward, and preoperative ALT and AST levels, and a lower preoperative AST/ALT ratio and remifentanil and propofol doses, than those without PELE (Table 4). 5-ALA was more frequently used in patients with PELE. Multivariate analyses showed that significant predictive factors for PELE were 5-ALA treatment (odds ratio [95% confidence interval], 2.30 [1.14–4.67]; P = 0.021), preoperative ALT level (1.07 [1.02–1.11]; P = 0.002), BMI (1.13 [1.00–1.28]; P = 0.045), and MBP in the ward (1.05 [1.00–1.10]; P = 0.033) (Table 5). Among 95 patients treated with 5-ALA, 41 (43.2%) patients showed 70 PELEs. Postoperative elevation of ALT, AST, ALP, and T.BIL was shown in 39, 22, 5, and 4 patients respectively. Patients with PELE had a higher BMI, SBP and MBP in the ward, and preoperative ALT level than those without PELE (Table 6). Multivariate analysis showed that significant predictive factors for PELE were preoperative ALT level (odds ratio [95% confidence interval], 1.10 [1.04–1.17]; P = 0.001) and BMI (1.29 [1.08–1.56]; P = 0.006, Table 5). In the ROC analysis, the preoperative ALT value and BMI showed the area under the curve of 0.74 and 0.70, respectively (Figure 1). The optimal cut-off value for preoperative ALT was 27.5 U/L, and PELE developed more frequently in cases with preoperative ALT levels ≥ 28 U/L (9.26 [3.25–26.40]; P < 0.001). The optimal cut-off value for BMI was 23.8 m/kg^2, and PELE developed more frequently in cases with BMI ≥ 23.8 m/kg^2 (3.97 [1.67–9.40]; P = 0.002). When the cut-off value for BMI was 25 m/kg^2, PELE developed more frequently in cases with BMI > 25 m/kg^2 (3.00 [1.25–7.20]; P = 0.014). BMI was positively correlated with preoperative serum ALT levels (correlation coefficient: 0.289; P = 0.005)

Serial changes in liver enzymes during the study period are shown in Figure 2. Significant group-time interactions were observed for ALT and ALP, but not for AST and

T.bil. (P = 0.001, <0.001, 0.061 and 0.568 for ALT, ALP, AST, and T.bil, respectively). In patients treated with 5-ALA, the ALT value at T2, T3, T4, T5, and T6 was higher than the preoperative baseline (P < 0.01, respectively). In patients treated with 5-ALA, 39 patients had maximum postoperative ALT levels > 40 U/L, and their ALT value returned to the normal value (<40 U/L) in one (2.6%), four (10.3%), eight (20.5%), and 23 (59.0%) patients at T3, T4, T5, and T6, respectively. Three patients had ALT levels > 40 U/L at T6, with a downward trend.

Discussion

In this clinical report, 62 (34.6%) patients showed 99 episodes of PELE. Postoperative ALT elevation was observed the most frequently and followed by AST, ALP, and T.bil elevation. Four (4.2%) patients treated with 5-ALA, showed grade 3 elevation of transaminases based upon CTCAE of investigations. 5-ALA treatment was predictive of PELE. In all patients undergoing brain tumor surgery, as well as those treated with 5-ALA, preoperative ALT level and BMI, were independent risk factors for PELE.

5-ALA is used to facilitate high-grade glioma resection, but it can increase postoperative liver enzymes due to its hepatotoxic effect. In this study, the use of 5-ALA was associated with PELE, with an odds ratio of 2.3. Similarly, previous studies have documented transient and self-limiting liver enzyme abnormalities after the use of 5-ALA [5, 9, 14, 15, 26]. Exogenous loading of 5-ALA bypasses the rate-limiting step of heme synthesis, leading to PpIX accumulation in lesions in the skin and other tissues. Because of its high molecular weight and hydrophilic characteristics, PpIX cannot be excreted by the kidney; its excretion is solely dependent on the hepatobiliary system. Large amounts of PpIX can be hepatotoxic, resulting in PELE [20].

The CTCAE is used to categorize liver enzyme levels into four grades based on the extent of adverse effects [21]. In this study, the overall incidence of PELE was 34.6%. Specifically, the incidence of PELE was 43.2% in patients treated with 5-ALA and 25.0% in those without 5-ALA administration. Similarly, in a previous report, the incidence of 5-ALA–induced temporary PELE was 42% [15]. Another previous study showed that preoperative 5-ALA administration resulted in significant increases in the incidence of postoperative elevation of ALT (36.5%), GGT (37.7%), AST (19.2%), and T.bil (5.4%), levels [26]. More importantly, four (4.2%) patients treated with 5-ALA showed grade 3 elevation of liver enzymes (ALT, $n = 3$; ALT and AST, $n = 1$) during the early postoperative period. However, their ALT and AST levels returned to preoperative baseline levels (<ULN) on PODs 15–45. Similarly, Stummer et al.[23] observed grade 3 elevation of liver enzymes in 3 (5.8%) of 52 patients on POD 7, which resolved to grade 1 or 2 on POD 14.

Notably, our study showed PELE in up to 25% of patients without 5-ALA administration. This finding suggests that PELE is associated with factors other than 5-ALA use. Previous clinical studies have shown that PELE can result from various factors, such as anesthesia, surgery, and use of medications such as antibiotics and anti-epileptics [7, 10, 16, 17]. In this study, all patients were anesthetized with propofol. A previous report showed that propofol resulted in concentration-dependent inhibition of cytochrome P450 enzyme in the liver, and may therefore alter the metabolism of drugs that depend on this enzyme [4]. Moreover, because it reduces blood flow to the liver, other drugs metabolized in the liver may be eliminated slowly, thereby causing more hepatotoxicity [12]. In addition to propofol, dexamethasone, anti-epileptic drugs, and cefazolin are known to be associated with liver enzyme elevation [2, 3, 29]. In this study, all three drugs were administered preoperatively, which may in part explain the occurrence of PELE.

The time profile of the ALT level after brain tumor surgery is likely to be different

between patients treated with 5-ALA and those without. In patients with 5-ALA administration, ALT levels were significantly higher than the preoperative baseline from POD 1 to POD 45 with a peak on POD 3-6. On PODs 15–45, these levels returned to the normal value (<40 U/L) in most patients. Specifically, of 39 patients treated with 5-ALA whose maximum postoperative ALT levels > 40 U/L, 13 and 36 patients showed the normal value of serum ALT on PODs 6 and 14, respectively. Only three patients showed ALT elevation > 40 U/L on PODs 15–45, with a downward trend. Consistent with our results, previous studies investigating 5-ALA–induced hepatobiliary dysfunction showed similar changes in liver enzymes during the postoperative period [15, 23, 24, 26, 27].

In this study, the preoperative ALT level was a significant predictive factor for PELE after brain tumor surgery, regardless of 5-ALA treatment. In the subgroup of patients treated with 5-ALA, ALT levels ≥ 28 U/L increased the risk of PELE approximately 9.3-fold. In addition, preoperative AST level was higher and preoperative AST/ALT ratio was lower in patients with PELE, although these variables were not significant predictive factors in multivariate analysis. Although these findings are not surprising, they suggest the need to pay particular attention to postoperative liver enzyme levels in patients with high preoperative transaminase levels, who are vulnerable to the development of PELE after brain tumor surgery.

This study showed that BMI was associated with PELE in patients undergoing brain tumor surgery, irrespective of 5-ALA treatment. In the subgroup of patients treated with 5-ALA, patients with BMI ≥ 23.8 and > 25 m/kg^2 had a 4.0- and 3.0-fold higher risk of PELE development, respectively. A possible explanation for such findings was that BMI was strongly associated with serum level of liver enzymes, especially ALT. High BMI is known to be a significant independent risk factor for elevated serum ALT level [10]. In addition, a previous study showed a significant correlation between BMI and the extent of

hepatic steatosis [18]. Therefore, patients with high BMI have a high chance of preoperative upper normal value of serum ALT due to hepatic steatosis, which may be in part responsible for PELE in such patients.

This study showed that the MBP measured in the ward was associated with PELE. Patients with preoperative MBP > 87.5 mmHg had a 2.8-fold higher risk of PELE development. A possible explanation for this finding is that patients with preoperative MBP > 87.5 mmHg were more susceptible to relative intraoperative hypotension, which may have caused hepatocellular injury by ischemia. Intraoperative MBP decreased more significantly from pre-operative MBP in patients with pre-operative MBP > 87.5 mmHg (by 19 mmHg) than in those with pre-operative MBP < 87.5 mmHg (by 7 mmHg). Although intraoperative MBP did not differ between patients with and without PELE, such relative changes in MBP may cause hepatocellular injury. Hepatic blood flow is significantly reduced during hypotension, especially during general anesthesia, due to the unique blood supply and regulatory mechanism [16]. In addition, ample evidence shows that hypertensive patients tend to have right-shifted autoregulation curves (higher blood pressure), and are therefore less tolerant of low blood pressure [19]. Taken together, these findings suggest that maintaining appropriate intraoperative MBP will help to decrease the occurrence of PELE in patients undergoing brain tumor surgery, especially those with high preoperative MBPs.

Our result showed that 5-ALA was more frequently used in patients with PELE than those without (66.1 vs. 46.2%, a mean difference of 19.9%). In the post-hoc sample size calculation based upon our result, 74 patients for the PELE group and 140 for the no PELE group were needed to achieve statistical significance with $\alpha = 0.05$ and $\beta = 0.2$. Therefore, the post-hoc power analysis showed that the number of patients enrolled in each group was inadequate in this study.

In this study, patients with preoperative 5-ALA administration showed significantly lower intraoperative MBP and higher intraoperative lactate levels. Similarly, Chung and Eljamel reported that 11% of patients who received 5-ALA developed hypotension, which was defined as a drop of MBP by 20 mmHg or more within 3 hours of post-administration [5]. Several studies showed elevated baseline and intraoperative lactate levels in patients with high-grade brain tumors because of the Warburg effect [1, 6, 13]. Such findings may partly explain high intraoperative lactate levels shown in the 5-ALA group because there are many high-grade glioma patients in the 5-ALA group.

This study has some limitations. First, because of its retrospective design, unavoidable biases could have affected the results. Second, we measured only four liver enzymes (ALT, AST, ALP, and T.bil). GGT is known to be a surrogate marker of cholestatic liver injury, and previous studies have documented temporary postoperative elevation of GGT in patients with 5-ALA administration [15, 26]. Although the GGT level is indicative of liver function, it is not routinely measured in patients with brain tumors during postoperative periods in our clinical practice. Thus, we did not examine the effect of 5-ALA on postoperative GGT levels in this study. In addition, we did not measure plasma PpIX level, which results in damage to cholangiocytes and hepatocytes. Therefore, we had limitations in revealing the pathophysiology of 5-ALA-induced PELE associated with plasma PpIX level. Third, patients with preoperative elevation of liver enzymes were excluded because this condition could bias the interpretation of 5-ALA–induced PELE; thus, we did not examine the toxic hepatobiliary effect of 5-ALA in patients with preoperative liver enzyme elevation. Fourth, because a fixed dose (20 mg/kg) of 5-ALA was used in this study, we did not evaluate the dose-dependent effects of 5-ALA on PELE. Fifth, caution is necessary when interpreting predictive factors associated with PELE because the predictive model has relatively weak explanatory power, which indicates that

some clinically significant risk factors may have been missed. Also, some preoperative and intraoperative variables, which are able to act as confounders, showed a significant difference between PELE and no PELE group, although they were adjusted in multivariate analysis. A propensity score matching of these variables between the two groups may strengthen our main findings. More importantly, a sample size was relatively small in this study. A further large-scaled investigation is needed to identify significant predictive factors of PELE especially when 5-ALA is used in brain tumor surgery. Finally, whether the extent of PELE associated with the use of 5-ALA is clinically relevant remains questionable. Although the use of 5-ALA was associated with increased PELE development, the incidence of grade 3 elevation of liver enzymes was very low and the maximum values of ALT and AST were within a range of 5×ULN to 8×ULN in this study. A previous study showed that liver damage by ischemia or other forms of liver damage were characterized by much higher concentrations of liver enzymes (e.g., aminotransferase: >10×ULN to >50×ULN in ischemia, >10×ULN in toxic injury, 5-10×ULN to >10×ULN in acute viral hepatitis) [8].

Conclusions

The use of 5-ALA for brain tumor surgery was associated with an increased incidence of PELE, especially ALT elevation, but a low incidence of severely elevated liver transaminases levels in patients with preoperative normal values of liver enzymes. Although 5-ALA caused a substantial increase in serum ALT level during the early postoperative period, this elevation was mostly transient and self-limited. Overall, these findings suggested that the use of 5-ALA is relatively safe for brain tumor surgery. In subgroup analysis, preoperative ALT level and BMI were associated with PELE in patients

treated with 5-ALA. Therefore, when 5-ALA is administered to patients with the upper normal value of serum ALT and overweight, attention is paid to PELE.

Table 1. Comparisons of demographic and preoperative laboratory and hemodynamic data in patients with versus without 5-ALA administration

	5-ALA (n = 95)	No 5-ALA (n = 84)	*P* value
Age	54.0 ± 13.7	53.7 ± 16.0	0.900
Male gender (n, %)	59 (62.1%)	42 (50.0%)	0.103
Body mass index (m/kg^2)	24.2 ± 3.2	23.8 ± 3.0	0.414
ASA class (n, %)			0.430
I	24 (25.3%)	25 (29.8%)	
II	57 (60.0%)	42 (50.0%)	
III	14 (14.7%)	16 (19.0%)	
IV	0 (0.0%)	1 (1.2%)	
Comorbidity (n, %)			
Previous craniotomy	17 (17.9%)	7 (8.3%)	0.098
Cerebrovascular	3 (3.2%)	5 (6.0%)	0.477
Cardiac	4 (4.2%)	7 (8.3%)	0.352
Pulmonary	11 (11.6%)	21 (25.0%)	0.032
Diabetes	8 (8.4%)	15 (17.9%)	0.097
Hypertension	22 (23.2%)	25 (29.8%)	0.405
Hepatic	0 (0.0%)	1 (1.2%)	0.469
Renal	1 (1.1%)	1 (1.2%)	1.000
Extracranial malignancy	7 (7.4%)	27 (32.1%)	< 0.001
Others	6 (6.3%)	8 (9.5%)	0.604
Preoperative ALT (U/L)	22.1 ± 9.0	19.8 ± 8.8	0.088
Preoperative AST (U/L)	19.6 ± 5.9	19.0 ± 6.1	0.480
Preoperative ALP (U/L)	62.9 ± 15.0	61.5 ± 15.4	0.541

Preoperative T.bil (mg/dL)	0.6 ± 0.2	0.6 ± 0.2	0.194
Preoperative Hg (g/dL)	14.0 ± 1.3	13.4 ± 1.3	0.002
Average SBP at ward (mmHg)	118.8 ± 11.3	120.5 ± 11.7	0.319
Average MBP at ward (mmHg)	88.0 ± 8.0	89.0 ± 8.5	0.396

5-ALA, 5-aminolevulinic acid; ASA, American Society of Anesthesiologists; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; T.bil, total bilirubin; Hg, hemoglobin; SBP, systolic blood pressure; MBP, mean blood pressure.

Table 2. Comparisons of intraoperative hemodynamic and postoperative laboratory data in patients with versus without 5-ALA administration

	5-ALA (n = 95)	No 5-ALA (n = 84)	*P* value
Anesthesia duration (min)	316.9 ± 76.5	309.9 ± 106.8	0.609
Operation duration (min)	253.5 ± 69.8	242.3 ± 98.7	0.378
Propofol (mg/kg/hr)	8.8 ± 1.9	8.5 ± 1.4	0.238
Remifentanil (ug/kg/hr)	8.7 ± 1.8	8.7 ± 2.4	0.885
Fluid balance (ml)	357.4 ± 636.4	169.7 ± 737.1	0.081
Average SBP during operation (mmHg)	111.0 ± 9.0	111.8 ± 8.4	0.547
Average MBP during operation (mmHg)	73.8 ± 6.6	77.2 ± 6.2	0.001
Maximal lactate during operation (mmol/L)	2.2 ± 1.1	1.8 ± 0.8	0.006
Maximal glucose during operation (mg/dL)	144.5 ± 24.2	141.6 ± 29.1	0.464
Vasopressor use (n, %)	78 (82.1%)	66 (78.6%)	0.552
Continuous phenylephrine infusion (n, %)	58 (61.1%)	40 (47.6%)	0.072
Pathologic diagnosis (n, %)			
Astrocytoma	16 (16.8%)	2 (2.4%)	0.001
Ependymoma	1 (1.1%)	4 (4.8%)	0.188
Glioma	8 (8.4%)	1 (1.2%)	0.038
Glioblastoma	55 (57.9%)	1 (1.2%)	<0.001
Hemangiocytoma	0 (0.0%)	3 (3.6%)	0.101
Hemangioblastoma	0 (0.0%)	2 (2.4%)	0.219
Meningioma	1 (1.1%)	35 (41.7%)	<0.001
Metastatic tumor	2 (2.1%)	26 (31.0%)	<0.001
Neurocytoma	1 (1.1%)	1 (1.2%)	1.000
Oligodendroglioma	10 (10.5%)	0 (0.0%)	0.002
Schwannoma	0 (0.0%)	7 (8.3%)	0.004
Inflammation	1 (1.1%)	2 (2.4%)	0.601
Maximal postoperative ALT (U/L)	53.4 ± 53.3	29.3 ± 20.4	< 0.001

Maximal post-op ALT > 40 U/L (n, %)	39 (41.1%)	17 (20.2%)	0.005
CTCAE of hepatobiliary toxicity			
Grade 1	32 (33.7%)	16 (19.0%)	0.042
Grade 2	3 (3.2%)	1 (1.2%)	0.624
Grade 3	4 (4.2%)	0 (0.0%)	0.124
Maximal postoperative AST (U/L)	36.8 ± 36.6	27.8 ± 21.5	0.045
Maximal post-op AST > 40 U/L (n, %)	22 (23.2%)	12 (14.3%)	0.187
CTCAE of hepatobiliary toxicity			
Grade 1	18 (18.9%)	11 (13.1%)	0.391
Grade 2	3 (3.2%)	1 (1.2%)	0.624
Grade 3	1 (1.1%)	0 (0.0%)	1.000
Maximal postoperative ALP (U/L)	68.7 ± 28.3	60.8 ± 18.4	0.029
Maximal post-op ALP > 118 U/L (n, %)	5 (5.3%)	0 (0.0%)	0.093
CTCAE of hepatobiliary toxicity			
Grade 1	5 (5.3%)	0 (0.0%)	0.061
Grade 2	0 (0.0%)	0 (0.0%)	NA
Grade 3	0 (0.0%)	0 (0.0%)	NA
Maximal postoperative T.bil (mg/dL)	0.8 ± 0.3	0.7 ± 0.2	< 0.001
Maximal post-op T.bil > 1.3 mg/dL (n, %)	4 (4.2%)	0 (0.0%)	0.124
CTCAE of hepatobiliary toxicity			
Grade 1	3 (3.2%)	0 (0.0%)	0.249
Grade 2	1 (1.1%)	0 (0.0%)	1.000
Grade 3	0 (0.0%)	0 (0.0%)	NA

5-ALA, 5-aminolevulinic acid; SBP, systolic blood pressure; MBP, mean blood pressure; CTCAE, common terminology criteria for adverse events; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; T.bil, total bilirubin; NA, non-applicable.

Table 3. Comparison of postoperative laboratory data between patients with postoperative elevation of liver enzymes (PELE) and those without

	PELE (n = 62)	No PELE (n = 117)	*P* value
Post-op ALT			
Maximal post-op ALT (U/L)	58.0 (48.0–83.8)	22.0 (17.0–30.5)	< 0.001
Maximal post-op ALT > 40 U/L (n, %)	56 (90.3%)	0 (0.0%)	< 0.001
Maximal post-op ALT (U/L)	63.5 (50.0–88.3)	No value	NA
CTCAE of investigations			
Grade 1	48 (77.4%)	0 (0.0%)	< 0.001
Grade 2	4 (6.5%)	0 (0.0%)	0.013
Grade 3	4 (6.5%)	0 (0.0%)	0.013
Post-op AST			
Maximal post-op AST (U/L)	42.0 (28.5–69.8)	20.0 (16.0–24.0)	< 0.001
Maximal post-op AST > 40 U/L (n, %)	34 (54.8%)	0 (0.0%)	< 0.001
Maximal post-op AST (U/L)	61.5 (44.0–96.3)	No value	NA
CTCAE of investigations			
Grade 1	29 (46.8%)	0 (0.0%)	< 0.001
Grade 2	4 (6.5%)	0 (0.0%)	0.013
Grade 3	1 (1.6%)	0 (0.0%)	0.346
Post-op ALP			
Maximal post-op ALP (U/L)	68.0 (57.0–82.3)	58.0 (47.0–70.5)	< 0.001
Maximal post-op ALP > 118 U/L (n, %)	5 (8.1%)	0 (0.0%)	0.004
Maximal post-op ALP (U/L)	157.0 (138.5–194.5)	No value	NA
CTCAE of investigations			

Grade 1	5 (8.1%)	0 (0.0%)	0.004
Grade 2	0 (0.0%)	0 (0.0%)	NA
Grade 3	0 (0.0%)	0 (0.0%)	NA
Post-op T.bil			
Maximal post-op T.bil (mg/dL)	0.7 (0.6–1.0)	0.7 (0.5–0.9)	0.075
Maximal post-op T.bil > 1.3 mg/dL (n, %)	4 (6.5%)	0 (0.0%)	0.013
Maximal post-op T.bil (mg/dL)	1.5 (1.4–1.9)	No value	NA
CTCAE of investigations			
Grade 1	3 (4.8%)	0 (0.0%)	0.040
Grade 2	1 (1.6%)	0 (0.0%)	0.346
Grade 3	0 (0.0%)	0 (0.0%)	NA
Post-op ASL/ALT ratio			
Immediate post-op	0.89 (0.67–1.29)	1.00 (0.80–1.36)	0.069
POD 1	0.85 (0.71–1.37)	1.13 (0.84–1.50)	0.010
POD 2	0.66 (0.48–1.06)	0.91 (0.69–1.13)	< 0.001
PODs 3–6	0.61 (0.44–0.77)	0.81 (0.65–1.00)	< 0.001
PODs 7–14	0.63 (0.45–0.88)	0.81 (0.65–1.00)	< 0.001
PODs 14–45	0.81 (0.62–1.17)	1.00 (0.70–1.30)	0.052

Data are expressed as number (%) or median (IQR). Post-op, postoperative; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; T.bil, total bilirubin; NA, non-applicable; POD, postoperative day

Table 4. Comparisons of demographic, preoperative laboratory, and pre- and intraoperative hemodynamic data in all patients with versus without postoperative elevated liver enzymes

	PELE in all patients		*P* value
	Yes (n = 62)	No (n = 117)	
Age	55.5 (43.5–62.0)	57.0 (43.5–67.0)	0.166
Male gender (n, %)	38 (61.3%)	63 (53.8%)	0.425
Body mass index (m/kg^2)	24.5 (23.3–26.7)	23.4 (21.2–25.0)	0.001
Body mass index > 25 m/kg^2 (n, %)	29 (50.0%)	29 (24.8%)	0.005
ASA class (n, %)			0.637
I	17 (27.4%)	32 (27.4%)	
II	37 (59.7%)	62 (53.0%)	
III	8 (12.9%)	22 (18.8%)	
IV	0 (0.0%)	1 (0.9%)	
Comorbidity (n, %)			
Previous craniotomy	11 (17.7%)	13 (11.1%)	0.313
Cerebrovascular	4 (6.5%)	4 (3.4%)	0.451
Cardiac	5 (8.1%)	6 (5.1%)	0.517
Pulmonary	10 (16.1%)	22 (18.8%)	0.811
Diabetes	7 (11.3%)	16 (13.7%)	0.827
Hypertension	21 (33.9%)	26 (22.2%)	0.132
Hepatic	0 (0.0%)	1 (0.9%)	1.000
Renal	1 (1.6%)	1 (0.9%)	1.000
Extracranial malignancy	9 (14.5%)	25 (21.4%)	0.362
Others	5 (8.1%)	9 (7.7%)	1.000
Pathologic diagnosis (n, %)			
Astrocytoma	6 (9.7%)	12 (10.3%)	1.000
Ependymoma	3 (4.8%)	2 (1.7%)	0.343
Glioma	4 (6.5%)	5 (4.3%)	0.500

Glioblastoma	23 (37.1%)	33 (28.2%)	0.293
Hemangiocytoma	1 (1.6%)	2 (1.7%)	1.000
Hemangioblastoma	0 (0.0%)	2 (1.7%)	0.545
Meningioma	8 (12.9%)	28 (23.9%)	0.120
Metastatic tumor	8 (12.9%)	20 (17.1%)	0.604
Neurocytoma	2 (3.2%)	0 (0.0%)	0.119
Oligodendroglioma	5 (8.1%)	5 (4.3%)	0.318
Schwannoma	2 (3.2%)	5 (4.3%)	1.000
Inflammation	0 (0.0%)	3 (2.6%)	0.552
Preoperative Hb (g/dL)	14.1 (13.2–15.0)	13.6 (12.8–14.6)	0.017
Intraoperative transfusion (n, %)	0 (0.0%)	1 (0.9%)	1.000
Immediate postoperative Hb (g/dL)	11.7 ± 1.6	11.0 ± 1.6	0.014
Postoperative transfusion (n, %)	6 (9.7%)	13 (11.1%)	0.967
Preoperative ALT (U/L)	24.5 (17.8–33.3)	17.0 (13.0–23.5)	<0.001
Preoperative AST (U/L)	20.0 (16.8–24.0)	18.0 (15.0–20.5)	0.002
Preoperative AST/ALT ratio	0.87 (0.70–1.11)	1.00 (0.75–1.29)	0.011
Preoperative ALP (U/L)	65.2 ± 16.6	60.7 ± 14.2	0.061
Preoperative T.bil (mg/dL)	0.6 (0.5–0.7)	0.6 (0.4–0.8)	0.984
Average SBP at ward (mmHg)	122.5 ± 11.3	118.0 ± 11.3	0.014
Average MBP at ward (mmHg)	90.5 (85.3–98.4)	86.0 (81.7–92.5)	0.001
Anesthesia duration (min)	312.5 (248.8–368.8)	300.0 (252.5–345.0)	0.439
Operation duration (min)	245.0 (183.8–305.0)	235.0 (190.0–277.5)	0.640
5-ALA (n, %)	41 (66.1%)	54 (46.2%)	0.017
Propofol (mg/kg/hr)	8.1 (7.5–9.2)	8.7 (7.8–9.9)	0.022
Remifentanil (ug/kg/hr)	8.1 (7.5–9.1)	8.6 (7.7–10.3)	0.027
Fluid balance (ml)	376.4 ± 766.5	213.3 ± 644.2	0.151
Average SBP during operation (mmHg)	109.0 (106.0–116.3)	109.0 (105.0–116.5)	0.654

Average MBP during operation (mmHg)	75.5 (71.0–79.0)	76.0 (71.0–80.0)	0.491
Maximal lactate during operation (mmol/L)	2.0 (1.5–2.7)	2.0 (1.2–2.5)	0.211
Maximal glucose during operation (mg/dL)	139.0 (128.8–155.3)	138.0 (125.5–153.0)	0.738
Vasopressor use (n, %)	49 (79.0%)	95 (81.2%)	0.881
Continuous phenylephrine infusion (n, %)	36 (58.1%)	62 (53.0%)	0.623

PELE, Postoperative elevated liver enzymes; ASA, American Society of Anesthesiologists; Hb, hemoglobin; AST; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; T.bil, total bilirubin; SBP, systolic blood pressure; MBP, mean blood pressure; 5-ALA, 5-aminolevulinic acid.

Table 5. Univariate and multivariate analyses for predictive factors associated with postoperative elevated liver enzymes

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	P value	Odds ratio	95% CI	P value
Postoperative elevated liver enzymes in all patients*						
Body mass index (kg/m2)	1.21	1.08–1.35	0.001	1.13	1.00-1.28	0.045
Meningioma	0.47	0.20–1.11	0.084			
Hypertension	1.79	0.91–3.55	0.094			
Propofol (mg/kg/h)	0.81	0.66–0.99	0.038			
Remifentanil (μg/kg/h)	0.86	0.74–1.01	0.058			
Average MBP at ward (mmHg)	1.07	1.03–1.11	0.001	1.05	1.00-1.10	0.033
5-ALA	2.28	1.20–4.32	0.012	2.30	1.14-4.67	0.021
Preoperative Hb (g/dL)	1.36	1.06–1.74	0.014			
Preoperative ALT (U/L)	1.09	1.05–1.13	<0.001	1.07	1.02-1.11	0.002
Preoperative AST (U/L)	1.09	1.03–1.15	0.003			
Preoperative AST/ALT ratio	0.32	0.13–0.77	0.011			
Preoperative ALP (U/L)	1.02	1.00–1.04	0.064			
Postoperative elevated liver enzymes in 5-ALA-treated patients†						
Body mass index (kg/m2)	1.23	1.10-1.53	0.002	1.29	1.08-1.56	0.006
ASA class (n,%)			0.095			
I	Ref.					
II	0.90	0.35–2.34	0.829			
III	0.17	0.03–0.91	0.039			
Preoperative Hb (g/dL)	1.30	0.95–1.78	0.102			
Average MBP at ward (mmHg)	1.09	1.03–1.15	0.003			
Preoperative ALT (U/L)	1.11	1.05–1.17	0.001	1.10	1.04-1.17	0.001
Preoperative AST (U/L)	1.07	1.00–1.16	0.062			

Preoperative AST/ALT ratio	0.22	0.06–0.75	0.016

ASA, American Society of Anesthesiologists; Hb, hemoglobin; MBP, mean blood pressure; 5-ALA, 5-aminolevulinic acid; ALT, alanine transaminase; AST,aspartatetransaminase

*In multivariate analysis with the forward stepwise conditional method, meningioma, hypertension, propofol and remifentanil infusion rates, preoperative hemoglobin concentration, preoperative AST and ALP levels, and preoperative AST/ALT ratio were adjusted. Nagelkerke R^2 statistic in step 4 is 0.254. Hosmer and Lemeshow goodness of fit test in step 4 is not significant at 5% (P =0.607).

†In multivariate analysis with the forward stepwise conditional method, ASA class, preoperative and immediate postoperative hemoglobin concentrations, average MBP at ward, preoperative AST level, and preoperative AST/ALT ratio were adjusted. Nagelkerke R^2 statistic in step 3 is 0.375. Hosmer and Lemeshow goodness of fit test in step 3 is not significant at 5% (P =0.453)

Table 6. Comparisons of demographic, preoperative laboratory, and pre- and intraoperative hemodynamic data in 5-ALA treated patients with versus without postoperative elevated liver enzymes

	PELE in 5-ALA treated patients		*P* value
	Yes (n = 41)	No (n = 54)	
Age	52.0 ± 11.6	55.5 ± 15.0	0.203
Male gender (n, %)	28 (68.3%)	31 (57.4%)	0.384
Body mass index (m/kg^2)	25.5 ± 3.4	23.3 ± 2.7	0.001
Body mass index > 25 m/kg^2 (n, %)	20 (48.8%)	13 (24.1%)	0.022
ASA class (n, %)			0.060
I	12 (29.3%)	12 (22.2%)	
II	27 (65.9%)	30 (55.6%)	
III	2 (4.9%)	12 (22.2%)	
Comorbidity (n, %)			
Previous craniotomy	8 (19.5%)	9 (16.7%)	0.930
Cerebrovascular	1 (2.4%)	2 (3.7%)	1.000
Cardiac	1 (2.4%)	3 (5.6%)	0.631
Pulmonary	3 (7.3%)	8 (14.8%)	0.340
Diabetes	1 (2.4%)	7 (13.0%)	0.132
Hypertension	12 (29.3%)	10 (18.5%)	0.325
Renal	1 (2.4%)	0 (0.0%)	0.432
Extracranial malignancy	2 (4.9%)	5 (9.3%)	0.695
Others	3 (7.3%)	3 (5.6%)	1.000
Pathologic diagnosis (n, %)			
Astrocytoma	5 (12.2%)	11 (20.4%)	0.408
Ependymoma	1 (2.4%)	0 (0.0%)	0.432

Glioma	4 (9.8%)	4 (7.4%)	0.723
Glioblastoma	22 (53.7%)	33 (61.1%)	0.604
Hemangiocytoma	0 (0.0%)	0 (0.0%)	NA
Hemangioblastoma	0 (0.0%)	0 (0.0%)	NA
Meningioma	1 (2.4%)	0 (0.0%)	0.432
Metastatic tumor	2 (4.9%)	0 (0.0%)	0.184
Neurocytoma	1 (2.4%)	0 (0.0%)	0.432
Oligodendroglioma	5 (12.2%)	5 (9.3%)	0.741
Schwannoma	0 (0.0%)	0 (0.0%)	NA
Inflammation	0 (0.0%)	1 (1.9%)	1.000
Preoperative Hb (g/dL)	14.3 ± 1.4	13.8 ± 1.3	0.100
Intraoperative transfusion (n, %)	0 (0.0%)	1 (1.9%)	1.000
Immediate postoperative Hb (g/dL)	11.8 ± 1.7	11.1 ± 1.6	0.065
Postoperative transfusion (n, %)	3 (7.3%)	5 (9.3%)	1.000
Preoperative ALT (U/L)	26.3 ± 8.8	18.9 ± 7.7	< 0.001
Preoperative AST (U/L)	21.0 ± 6.3	18.6 ± 5.4	0.054
Preoperative AST/ALT ratio	0.78 (0.62–1.05)	1.00 (0.77–1.19)	0.005
Preoperative ALP (U/L)	65.1 ± 16.4	61.2 ± 13.8	0.212
Preoperative T.bil (mg/dL)	0.6 ± 0.2	0.6 ± 0.3	0.427
Average SBP at ward (mmHg)	122.1 ± 11.8	116.2 ± 10.3	0.011
Average MBP at ward (mmHg)	90.7 ± 8.7	85.8 ± 6.7	0.003
Anesthesia duration (min)	317.4 ± 66.6	316.8 ± 83.9	0.957
Operation duration (min)	251.9 ± 61.3	254.6 ± 76.2	0.853
Propofol (mg/kg/hr)	8.5 ± 1.9	9.1 ± 1.8	0.150
Remifentanil (ug/kg/hr)	8.6 ± 1.8	8.9 ± 1.8	0.427
Fluid balance (ml)	288.5 ± 744.1	408.3 ± 545.7	0.411
Average SBP during operation (mmHg)	110.9 ± 9.7	111.0 ± 8.5	0.972
Average MBP during operation (mmHg)	74.2 ± 6.4	73.4 ± 6.8	0.574

Maximal lactate during operation (mmol/L)	2.3 ± 1.1	2.2 ± 1.1	0.605
Maximal glucose during operation (mg/dL)	142.1 ± 24.1	143.7 ± 27.9	0.449
Vasopressor use (n, %)	33 (80.5%)	45 (83.3%)	0.930
Continuous phenylephrine infusion (n, %)	25 (61.0%)	33 (61.1%)	1.000

PELE, Postoperative elevated liver enzymes; ASA, American Society of Anesthesiologists; Hb, hemoglobin; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; T.bil, total bilirubin; SBP, systolic blood pressure; MBP, mean blood pressure; 5-ALA, 5-aminolevulinic acid.

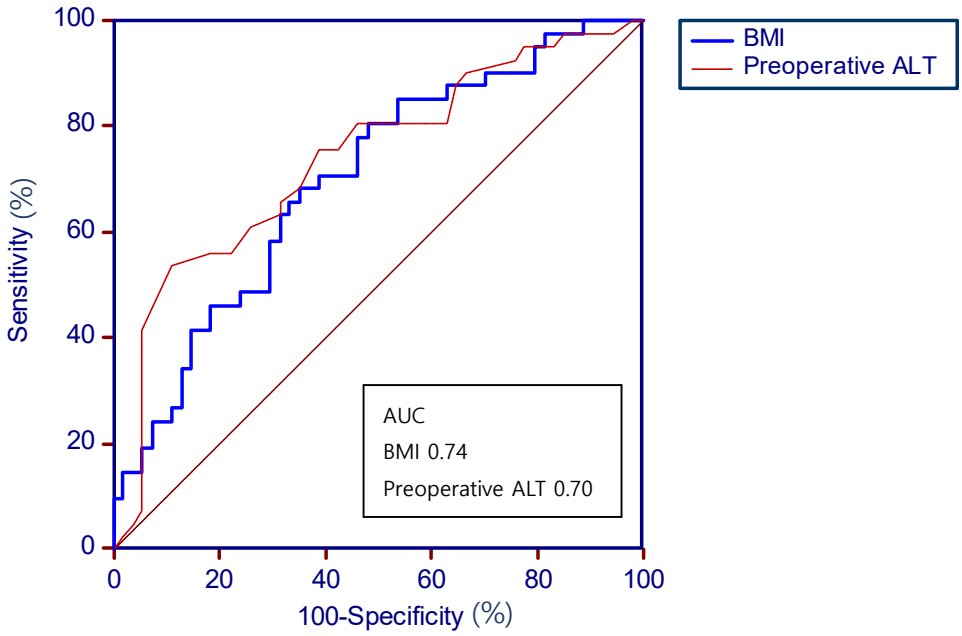

Figure 1. ROC curve of BMI and pre-op ALT on predicting PELE

ROC: receiver operating characteristics; BMI: body mass index; ALT: alanine transaminase; PELE: postoperative elevation of liver enzymes, AUC: area under curve

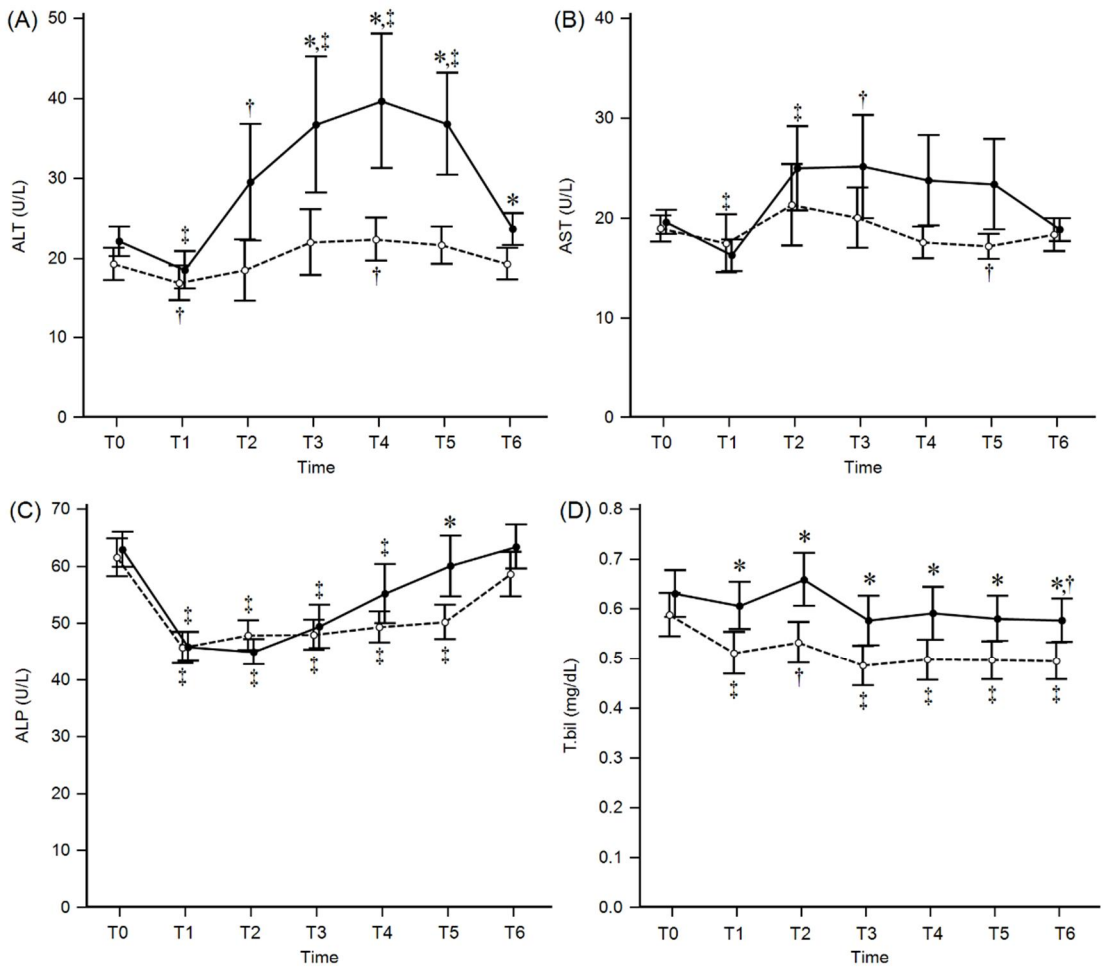

Figure 2. Comparisons of liver enzymes according to 5-ALA administration

5-ALA: 5-aminolevulinic acid, ALT: Alanine transaminase (A), AST: aspartate transaminase (B), ALP: alkaline phosphatase (C), T.bil: total bilirubin (D) in patients with (●, closed circle, solid line) versus without (○, open circle, broken line) 5-ALA administration. There were significant changes of ALT ($P = 0.001$) and ALP ($P < 0.001$) levels over time between the two groups, but not AST ($P = 0.061$) and T.bil. ($P = 0.568$) levels. *: $P \leq 0.007$ versus the no 5-ALA group, which indicates that there is a significant

difference even after compensating for multiple comparisons. †: $P < 0.05$ vs. T0 within group, ‡: $P < 0.01$ vs. T0 within group. T0: preoperative, T1: immediate postoperative, T2: postoperative day (POD) 1, T3: POD 2, T4: POD 3-6, T5: POD 7-14, T6: POD 15-45.

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요약 (국문초록)

배경: 뇌종양 수술에서 간효소 수치 상승은 5-aminolevulinic acid (5-ALA) 사용 이외의 원인으로도 생길 수 있다. 이 후향적 연구에서 우리는 수술 전 투여한 5-ALA가 수술 후 간효소 수치 상승과 관련이 있는지, 있다면 이러한 수치 상승을 예측할 수 있는 인자는 무엇인지를 알아보고자 하였다. 방법: 뇌종양 수술을 받는 환자들 중 수술 전 간효소 수치가 정상인 179명을 대상으로 수술 전부터 수술 후 45일까지 혈장 serum alanine transaminase(ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), total bilirubin (T.bil) 수치를 후향적으로 수집하였다. 결과: 5-ALA는 95명의 환자에서 투여되었고 (5-ALA군) 84명의 환자에서는 투여되지 않았다 (no 5-ALA군). 5-ALA군에서 유의하게 폐질환의 빈도가 높고 (11[11.6%] vs 21[25.0%], P = 0.032) 두개외 악성종양의 빈도가 높았다. (7[7.4%] vs 27[32.1%], P < 0.001). 수술 중 5-ALA 군의 젖산의 최대치가 더 높았고 (2.2 ± 1.1 vs 1.8 ± 0.8 mmol/L, P = 0.006) 평균혈압이 더 낮았다. (73.8 ± 6.6 vs 77.2 ± 6.2 mmHg, P = 0.001). 99건의 수술 후 간효소 수치 상승(ALT: 56, AST: 34, ALP: 5, and T.BIL: 4)이 62명(34.6%)의 환자에서 생겼다. 5-ALA를 투여받은 환자들 중 4명(4.2%)에서는 Common Terminology Criteria for Adverse Effects의 3단계에 해당하는 ALT의 상승이 보였다. 술 전 5-ALA의 투여는

술후 간효소 수치 상승의 원인이었다. (오즈비 [95%신뢰구간] 2.30 [1.14-4.67], P = 0.021) 5-ALA를 투여받은 환자(95명)에서 간효소 수치 상승은 70건(ALT, 39; AST, 22; ALP, 5; T.BIL, 4)이 41명(43.2%)에서 생겼다. 이 환자 군에서 간효소 수치상승의 유의한 예측인자는 술전 ALT 수치 (1.10 [1.04–1.17]; P = 0.001)와 체질량지수(1.29 [1.08–1.56]; P = 0.006)였다 ALT가 40 U/L 이상 상승했던 5-ALA 투여 환자는 39명이었다. 이들 중 13명은 14일째, 23명은 45일째 정상 수치로 회복되었다. 남은 3명은 45일째도 40 이상의 수치였지만 감소 추세였다. 결론: 수술 전 간효소 수치가 정상인 환자들에게 5-ALA을 사용하는 것은 일시적인 간수치 상승을 일으킬 수 있지만 간효소 수치가 심각하게 올라가는 환자들은 드물다. 정상치 상한의 간효소 수치나 비만인 환자들에게 5-ALA를 투여할 경우에는 수술 후 간효소 수치가 상승할 수 있음에 유의해야 할 것이다.

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주요어: 5-aminolevulinic acid. 뇌종양 수술. 간효소

학 번: 2015-30593